Please add the following new claims:

--34. (NEW) The composition according to claim 23, wherein the polynucleotide further comprises a promoter capable of expression in neurons.

B4

35. (NEW) The composition according to claim 34, wherein the polynucleotide further comprises an enhancer.--

REMARKS

Applicants respectfully request reconsideration and further examination in view of the following remarks.

Claims 1-19 and 21-35 are pending in this application. Claims 1-16 and 24-33 have been withdrawn from consideration as being drawn a nonelected invention. Claims 34 and 35 have been added. Support for claims 34 and 35 can be found in the specification, including at pages 6-7 and in original claim 23. Claims 17-19 and 23 were amended to more clearly define the claimed invention. This Amendment does not introduce new matter into the specification.

Double Patenting Rejections

The Office provisionally rejected claims 17 and 18 under 35 U.S.C. § 101 as allegedly claiming the same invention as that of claims 17 and 18 of copending application S.N. 09/501,787. (Paper No. 11, p. 4.) Applicants respectfully request that the Examiner hold this rejection in abeyance until allowable subject matter has been indicated.

The Office also provisionally rejected claims 19 and 21-23 under the judicially

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created doctrine of obviousness-type double patenting over claims 19 and 21-23 of copending application S.N. 09/501,787. (*Id.* at 4-5.) Applicants respectfully request that the Examiner hold this rejection in abeyance until allowable subject matter has been indicated.

Rejections Under 35 U.S.C. § 112, Second Paragraph

The Office rejected claims 17-19 and 21-23 under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention. (Paper No. 11, p. 6.) The Office asserted that the phrase "or a fraction thereof of at least 11 amino acid residues" in lines 2-3 of claims 17-18 is vague and renders the claims indefinite because it is unclear whether the fraction is a fraction of only fragment B or a fraction of the combination of fragment C and fragment B. (*Id.*)

Although applicants respectfully disagree, in an effort to expedite prosecution, claims 17 and 18 have been amended to recite "a fraction of fragment B having at least 11 amino acids . . . ." This amendment does not narrow the scope of claims 17 and 18 because it simply explains the claim as originally written. In other words, the "fraction thereof" recited in original claims 17 and 18 referred to a fraction of fragment B, as currently recited. Applicants respectfully request that this rejection be withdrawn.

Additionally, the Office asserted that the phrase "a polynucleotide encoding a protein or a polypeptide with a promoter . . . , and optionally an enhancer" in claim 23 is

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vague and renders the claim indefinite. (*Id.*) In an effort to expedite prosecution, applicants have amended claim 23 to recite:

> The composition according to claim 21, wherein the active molecule is a polynucleotide encoding a protein.

Applicants believe that in this context the terms "protein" and "polypeptide" are redundant and, therefore, have deleted the superfluous term "polypeptide" from the claim. The additional elements of original claim 23 (promoter and enhancer) have been included as part of new dependent claims 34 and 35, respectively. Therefore, the combined scope of amended claim 23 and new claims 34 and 35 is as broad as claim 23 prior to the amendment. Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 112, First Paragraph

1. Written Description

The Office rejected claim 19 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to reasonably convey to one skilled in the art, at the time the application was filed, that the inventors had possession of the claimed invention. (Paper No. 11, pp. 6-8.)

Claim 19 is directed to an "amino acid variant fragment of the hybrid fragment of tetanus toxin according to claim 17, wherein the variant fragment retains the capability of transferring *in vivo* a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse." The Office asserts that claim 19 "encompass[es]

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any amino acid variants that differ from the disclosed TTC via substitution, deletion or addition and . . . having the activity of TTC." (*Id.* at 7.) According to the Office, however, the specification fails to provide the structural features of TTC or its variants necessary for transferring a protein, peptide, or polynucleotiude through a neuromuscular junction and at least one synapse, as claimed. (*Id.*) Similarly, the Office asserts:

> Since the disclosure fails to describe common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the amino acid sequences of TTC as disclosed in the present application is insufficient to describe the genus.

(*Id.* at 8.) Applicants respectfully traverse this rejection.

The written description requirement for a claimed genus may be satisfied by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed invention. *See* M.P.E.P. § 2163, p. 2100-164. This is precisely what applicants have done here. Applicants have adequately described their claimed invention by combining both structural and functional characteristics.

Structurally, claim 19 is directed to an amino acid variant of the tetanus toxin hybrid fragment of claim 17. The hybrid fragment comprises a fragment C and a fragment B (or a fraction of fragment B having at least 11 amino acids). The specification explains that the combination of these fragments permits *in vivo* retrograde

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transport and transynaptic transport of biological molecules into the CNS. (Specification, p. 4.) The structure of these tetanus toxin fragments (B and C) is discussed in the specification and was well known in the art. (*See, e.g.*, Specification, pp. 2-4 and 8-9.)

Functionally, claim 19 recites that the variant fragment retains the capability of transferring *in vivo* a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse, just like the hybrid fragment of claim 17. Thus, claim 19 defines a claimed genus of structurally-related variants that possess a specific function.

Contrary to the Office's assertions, the claimed genus does possess a common attribute because the variants all derive from the structurally-defined hybrid fragment of claim 17. Furthermore, one of skill in the art would not expect substantial variation in the claimed variant tetanus toxin fragments because of the structurally-defined hybrid fragment and the recited functional language.

This case is similar to Example 9 of the U.S. PTO's "Synopsis of Application of Written Description Guidelines."[1] Example 9 addresses written description in the context of a hybridization claim. Specifically, the claim is directed to a nucleic acid that hybridizes to a specific sequence under stringent conditions and encodes a protein having a specific biological activity. The claim thus covers a genus of nucleic acids all of which hybridize with the recited sequence and encode a protein with specific activity.

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1 Exhibit 1, pp. 35-37.

In analyzing the written description support for this claimed genus, Example 9 states that

> a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention.

Example 9 concludes that the claimed invention is adequately described. For similar reasons, one of skill in the art would conclude that the structurally-defined hybrid fragment in combination with the recited functional language are adequate to determine that applicants were in possession of the claimed invention. Thus, the specification provides adequate written description support by disclosing relevant structural and functional characteristics of the claimed variant fragments. Accordingly, applications respectfully request withdrawal of this rejection.

2. Enablement

The Office also rejected claim 19 under 35 U.S.C. § 112, first paragraph, alleging that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. (Paper No. 11, pp. 8-11.) The Examiner acknowledges that the specification (*see, e.g.*, Specification, Example 1) enables one of skill in the art to make and use a hybrid fragment of tetanus toxin, which combines a tetanus toxin

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fragment with the B-galactosidase (β-gal)[2] protein ("the *lacZ*-TTC construct"), but asserts that the specification does not reasonably enable the full scope of the claims. (*Id.* at 8.) As with the written description rejection, the Office repeats that claim 19 "encompass[es] any amino acid variants that differ from the disclosed TTC via substitution, deletion or addition and includes various unknown and unidentified amino acid sequences having the activity of TTC." (*Id.* at 9.)

The Office further asserts that the

> specification also fails to provide adequate guidance and evidence how and which amino acid residue within [sic, the] TTC fragment can be deleted or substituted, or what amino acid residue can be added to [sic, the] TTC fragment such that the resulting amino acid variant still retain [sic] the activity of [sic, the] TTC fragment as disclosed.

(*Id.*) Finally, relying on various references,[3] the Office asserts that the relationship between protein structure and function is unpredictable. (*Id.* at 9-10.) Applicants respectfully traverse this rejection.

The Office asserts that the specification does not guide one of skill in the art to the specific deletions, substitutions and/or other variations that would yield variant hybrid tetanus toxin fragments retaining the transport capabilities of the hybrid fragment of claim 17. But the specification need not disclose, and preferably omits, what is well-known to those of skill in the art and already available to the public. *See* M.P.E.P. § 2164.05(a), p. 2100-180. Here, applicants disclose how to make and use a functional

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2 The β-gal protein is encoded by the *lacZ* gene.

3 The state of the prior art relevant to the enablement inquiry must be measured at the time the application was filed. M.P.E.P. § 2164.05. Thus, statements in the **1976** Rudinger reference, cited by the Office, has no bearing on the state of the art in 1997, when applicants filed their priority application.

TTC fragment (as acknowledged by the Examiner at page 8 of Paper No. 11); methods for generating variants or mutants, such as those of applicants' hybrid tetanus toxin fragments, were well-known;[4] applicants disclose how to make and use a construct for evaluating other functional, variant hybrid fragments; and applicants disclose a routine screening method to determine whether such variant hybrid fragments retain the activity of the TTC fragment.

As acknowledged by the Office, the specification enables one of skill in the art to make and use the *lacZ*-TTC construct. (Paper No. 11, p. 8.) This construct is particularly well-suited for screening variant hybrid fragments, which can simply replace the TTC fragment in the existing *lacZ*-TTC construct. The presence in the construct of a reporter gene, such as *lacZ*, allows one of skill in the art, following the Examples disclosed in the specification, to routinely screen variant constructs and determine whether they retain the transport properties of the *lacZ*-TTC construct. As disclosed in the specification, this can be accomplished, for example, by introducing the construct into the CNS and monitoring β-galactosidase activity.

Although such screening could conceivably involve numerous variant constructs, the test for "undue experimentation" is not merely quantitative. Thus, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. *See* M.P.E.P. § 2164.06, p. 2100-181.

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4 *See, e.g.*, Ling et al., *Approaches to DNA Mutagenesis: An Overview*, Anal. Biochem., 254(2):157-78 (1997) (Exhibit 2).

That is precisely the case here, where the specification provides hybrid tetanus toxin fragments and teaches that variant hybrid fragments thereof can be obtained using well-known techniques, as discussed above. The specification provides one of skill in the art with the tools to screen variants in a routine manner to determine whether they possess the capability of transferring *in vivo* a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse, as claimed. Accordingly, applicants respectfully request that this rejection under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

Claims 17-19 and 21-23 have been rejected under 35 U.S.C. § 103(a) as being unpatenable over Mueller, 1994 (Report, ARO-27890.1-LS, Order No. AD-A290 501, NTIS, p. 1-15) in view of Hohne-Zell et al., 1993 FEBS Letters, Vol. 336, No. 1, p. 175-180. (Paper No. 11, pp. 11-13.) The Office asserts Mueller teaches that fragment C of the tetanus toxin protein is a sufficient carrier molecule for mediating neuron-specific internalization and transport. (*Id.* at 12.) The Office acknowledges, however, that:

> Mueller does not teach a hybrid fragment comprising fragment C of tetanus toxin and at least 11 amino acid residues of fragment B or a hybrid fragment further comprises [sic, comprising] a fraction of a fragment A devoid of its toxic activity corresponding to zinc-binding motif between amino acid residues 225 and 245.

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(*Id.*) The Office alleges the secondary reference, Hohne-Zell, teaches that the putative zinc-binding domain contains the active site of the tetanus toxin light chain. (*Id.*) Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the reference (or references when combined) must teach or suggest all elements of the claim. *See* M.P.E.P. § 2143.

The Office's obviousness rejection is improper for at least the reason that the references do not teach or suggest all elements of the claimed invention. Claims 17 and 18 recite that the hybrid fragment includes a fragment B, or a fraction of fragment B having at least 11 amino acid residues. The remaining claims depend directly or indirectly from claim 17. Neither Mueller nor Hohne-Zell teaches or suggests a hybrid tetanus toxin fragment that includes fragment B, or a fraction thereof having at least 11 amino acid residues. Thus the cited references fail to teach or suggest all elements of the claimed invention.

Without citing any evidence, the Office asserts:

> It also would have been obvious for one of ordinary skill at the time of the invention to include a portion of fragment B with fragment C of tetanus toxin because the toxic region of tetanus toxin resides in the putative zinc-binding domain, which is at amino terminal, and inclusion of a portion of non-

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> toxic region of tetanus toxin would not contribute to the toxicity of tetanus toxin.

(*Id.* at 13.) This conclusory statement, however, does not remedy the deficiencies of Mueller and Hohne-Zell and is not a substitute for the evidence required to establish a *prima facie* case of obviousness. *See In re Zurko*, 258 F.3d 1379, 1385, 59 U.S.P.Q.2d 1693, 1697 (Fed. Cir. 2001) (finding that general conclusions about what one of ordinary skill in the art would have known cannot remedy the deficiencies of the references relied on by the Board). Accordingly, applicants respectfully request withdrawal of this 35 U.S.C. § 103 rejection.

CONCLUSION

In view of the foregoing remarks, applicants respectfully request the examination on the merits of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: April 10, 2003

By: 

Timothy B. Donaldson
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APPENDIX

IN THE SPECIFICATION:

At page 1, please amend the first paragraph as follows:

This is a continuation of application Serial No. 09/129,368, filed August 5, 1998, now abandoned, which is based on provisional application Serial No. 60/055,615, filed August 14, 1997, abandoned, and provisional application Serial No. 60/065,236, filed November 13, 1997, abandoned, all of which are incorporated by reference.

IN THE CLAIMS:

Please amend the claims as follows:

17. (Amended) A hybrid fragment of tetanus toxin comprising a fragment C and a fragment B or a fraction [thereof] of fragment B having at least 11 amino acid residues, wherein the hybrid fragment is capable of transferring *in vivo* a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse.

18. (Amended) A hybrid fragment of tetanus toxin comprising a fragment C and a fragment B or a fraction [thereof] of fragment B having at least 11 amino acid residues and a fraction of a fragment A devoid of its toxic activity corresponding to the proteolytic domain having a zinc-binding motif located in the central part of the chain between amino acids 225 and 245, wherein the hybrid fragment is capable of transferring *in vivo*

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a protein, a peptide or a polynucleotide through a neuromuscular junction and at least one synapse.

19. (Amended) An amino acid variant fragment of the hybrid fragment of tetanus toxin according to claim 17, wherein the variant fragment retains the capability of transferring *in vivo* a protein, a peptide, or a polynucleotide through a neuromuscular junction and at least one synapse [having the same properties as the hybrid fragment of tetanus toxin according to claim 17].

23. (Amended) The composition according to claim 21, wherein the active molecule is a polynucleotide encoding a protein [or a polypeptide with a promoter capable of expression in neurons, and optionally an enhancer].

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